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REMARKS

Claims 1-50, as amended by the Preliminary Amendment filed March 18, 1998, are pending.

The specification has been amended above to refer to the priority applications of the instant application, and their current status. The specification has also been amended to incorporate the Abstract of priority application PCT Application No. PCT/US94/04314. These amendments address informalities referred to in the Office Action, at page 2, paragraph 4, and do not introduce new matter. Therefore, entry of the above amendments is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-50 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The rejection is traversed for the reasons that follow.

The Office Action indicates that claims 1-50 are directed to methods for production of an organic molecules, and notes that the claims are generic with respect to the number and chemical composition of the reagents; with respect to the types and number of reactions; with respect to the method by which the chemical reaction steps are carried out; and with respect to the selection methods to isolate the desired organic molecule. The

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Office Action further notes that the claims encompass production of molecules including drugs, enzymes, and DNA molecules, and states that "[a]ll of these molecules could be made by the claimed methods..." Additionally, it is stated in the Office Action, with respect to the exemplified method of synthesis of a peptide library, that "[t]he selection method is very straightforward. One merely screens for a desired enzymatic activity."

Applicants agree with the characterization in the Office Action that all of the indicated molecules could be made by the claimed methods. Applicants also agree with the characterization in the Office Action that the described selection methods are very straightforward. Accordingly, it appears to be contradictory that it is subsequently stated in the Office Action that "...it would require undue experimentation to enable a reasonable number of organic molecule production methods."

In support of the assertion that it would require undue experimentation to practice the claimed methods, the Office Action states that "one would have to work out the details of how the multiple rounds of reactions are carried out, how the various reactants are brought into contact with the growing molecule, and how the waste products are washed away." In contrast to the statement in the Office Action, it is respectfully submitted that the specification provides all necessary details regarding the chemical reactions that provide for a highly diverse library of products from a starting group of organic molecules.

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First, the specification teaches the starting group of organic molecules to use. More specifically, the specification teaches that the starting compounds can include all organic compounds, including, for example, alkanes, alkenes, alkynes, alcohols, ethers, amines, aldehydes, ketones, acids, esters, amides, cyclic compounds, heterocyclic compounds, hetero-atom bearing compounds, amino acids and nucleotides (page 9, lines 19-24).

Second, the specification teaches the reactants that can be used to perform a series of diverse chemical reactions on the starting molecules. For example, the specification teaches that diverse chemical reactions can be catalyzed by exogenously added polypeptide enzymes, or other sets of candidate enzymes such as antibody libraries, protein libraries, nucleic acid molecule libraries, and libraries of core building blocks and adducts (page 20, line 9, to page 21, line 22). Where the chemical reactions are catalyzed by protein-based enzymes, the enzymes can include, for example, oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases (page 22, line 23, to page 23, line 12). Additionally, the specification teaches that diverse chemical reactions can be catalyzed by the population of substrates themselves (page 18, line 29, to page 19, line 4).

Alternatively, the specification teaches that the chemical reactions need not be catalyzed by enzymes. To perform the methods with respect to non-enzymatic reactions, the substrates can be reacted, for example, with dehydrating agents, reducing agents, oxidizing agents, heat or light. The

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specification provides examples of such agents and their uses (page 35, line 3, to page 37, line 24).

Third, the specification teaches the conditions under which the chemical reactions can be performed. For example, the specification provides guidance regarding reaction volumes, reactant concentrations and solubility considerations (page 23, line 13, to page 24, line 25); reaction times and temperatures (page 25, lines 14-16); and appropriate cofactors to add (page 25, lines 16-20) for performing the claimed methods with enzymes. The specification also provides guidance as to methods for separating catalysts from substrates, which can be useful for performing the enzymatic reactions sequentially (page 24, line 26, to page 25, line 14).

With respect to non-enzymatic methods for performing chemical reactions, the specification teaches appropriate conditions, such as solvents, reaction times, temperatures and pressures, for use with dehydrating agents, reducing agents, oxidizing agents, heat or light (page 35, line 3, to page 37, line 24).

By following the methods taught in the specification, the skilled person would arrive at a mixture containing a high diversity of organic molecules. Therefore, it is respectfully submitted that the specification adequately enables the generation of a high diversity of organic molecules according to the claimed methods.

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The Office Action further states that "one would have to develop selection schemes for diverse purposes" and that "one would have to work out the details of...how the desired product is isolated from the myriad exogenous products."

In contrast to the statement in the Office Action, it is respectfully submitted that the specification provides the necessary guidance to screen for and, if desired, to isolate, a molecule having a desired property from the diversity of products generated by the methods described above.

With respect to screening methods, the specification teaches that exemplary molecules of interest include molecules with the properties of acting as drugs, vaccines, liganding agents, catalysts, catalytic cofactors, structures of use, detector molecules and building blocks for other compounds (page 8, line 26, to page 9, line 18). The skilled person understands that the particular screening method will necessarily depend on the property of interest; however, given the guidance in the specification, and the extensive knowledge in the art regarding methods of screening for pharmaceutically and industrially useful compounds, the skilled person could have adapted such methods to any property of interest, without undue experimentation.

The specification teaches exemplary methods to identify low concentrations of receptor ligands from a mixture of molecules, by identifying the activation of cellular signaling pathways by the ligand (page 37, line 25, to page 38, line 30). Likewise, low concentrations of ligands can be identified by a

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variety of direct and competitive binding assays known in the art (page 39, line 10, to page 41, line 31). Receptor ligands can act by antagonizing, agonizing, substituting for, or modifying the effects of the natural hormone, and are thus candidate drugs for treatment of a variety of conditions (page 38, lines 12-16).

Additionally, the specification teaches an exemplary method of detecting a molecule with the property of inhibiting an enzymatic reaction, by screening the product mixture for inhibition of the enzymatic reaction of interest (page 42, lines 1-10). Similarly, the specification teaches that a molecule that is a catalyst, or cofactor, of a particular enzymatic reaction can be detected by determining the ability of the product mixture to cause an increase in production of the product of the catalyzed reaction (page 43, lines 5-8). Methods are well known in the art to prepare and detect chromogenic or fluorogenic reactants or products of an enzymatic reaction of interest, as well as to use antibody binding or shape complement techniques to identify such molecules (page 43, lines 12-21).

From a product mixture containing a molecule having a property of interest, the specification teaches methods for characterizing and/or isolating the molecule. For example, in order to determine the structure of the molecule of interest, the product mixture can be contacted with a solid support containing moieties that bind the molecule, such as a receptor or antibody. The molecules that are retained on the support can subsequently be freed in an isolated form. The structure of the molecule can

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then be determined by analytical means, such as mass spectroscopy and the like (page 43, line 27, to page 44, line 15).

Alternatively, the specification teaches that the product mixture can be winnowed to progressively smaller subsets, containing a higher concentration of the desired product, by reducing the set of initial substrates, or set of chemical reactions. The structural or functional properties of the product within the winnowed mixture can then be characterized and the product isolated (page 44, line 16, to page 47, line 21)

Applicants respectfully point out that practice of the methods of claims 1-24, 30-35, 37, and claims 39-50, insofar as they depend on claim 37, does not require isolation of the molecule having the activity of interest from the product mixture. It is sufficient for practice of the methods of these claims that the product having the desired property can be characterized, such that it can subsequently be produced by synthetic methods (page 47, line 22, to page 48, line 20). As set forth above, the specification teaches methods suitable either for characterizing or for isolating a molecule having a desired property from the product mixture.

Therefore, it is respectfully submitted that the specification enables selection and production of an organic molecule having a desired property.

In view of the above remarks, it is respectfully submitted that the specification adequately enables claims 1-50.

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Accordingly, removal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 1-50 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Jacobs et al., Trends Biochem. 12:19-26 (1994), which is a post-priority reference. The Office Action alleges that Jacobs et al. reviews prior art publications that describe certain elements of the claims, and that it would have been obvious to combine the various techniques of Jacobs et al. in order to screen large numbers of molecules of potential therapeutic value.

As stated in MPEP 706.02(j), 35 U.S.C. § 103 authorizes a rejection where, to meet the claim, it is necessary to modify a single reference or to combine it with one or more other references. After indicating that the rejection is under 35 U.S.C. § 103, the Examiner should set forth in the Office Action:

(A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column or page number(s) and line number(s) where appropriate,

(B) the difference or differences in the claim over the applied reference(s),

(C) the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter, and

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(D) an explanation of why one of ordinary skill in the art at the time the invention was made would have been motivated to make the proposed modification.

Jacobs et al. is a post-priority publication. It is respectfully submitted that the Office Action has not supported the allegation that the teachings referred to in Jacobs et al. are actually found in the prior art. It follows that the Office Action has also not set forth where in the prior art the relevant teachings are found. Nor has the Office Action indicated what are considered to be the differences in any of the 50 claims over the prior art, and proposed modifications over the prior art necessary to arrive at the claimed subject matter, and has not provided an explanation of motivation for one skilled in the art, at the time the invention was made, to make the proposed modification.

In the absence of specifically setting forth the grounds for rejection under 35 U.S.C. § 103, Applicants are unable to address the assertion that it would have been *prima facie* obvious to arrive at the claimed invention. Applicants respectfully request clarification of the grounds for rejection, with reference to teachings found in the prior art.

CONCLUSION

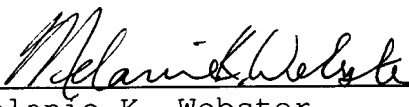
In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect.

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Should the Examiner have any questions, he is invited to call
Cathryn Campbell or the undersigned agent.

Respectfully submitted,

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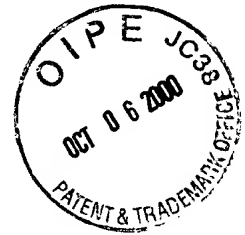
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By Melanie K. Webster
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September 29, 2000
Date of Signature